Disputes & Debates: Editors' Choice

Editors' Note: Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension

In their multicenter randomized controlled clinical trial of patients with idiopathic intracranial hypertension (IIH), Mollan et al. sought to determine the amount of weight loss necessary to achieve physiologic remission (intracranial pressure [ICP] ≤25 cm CSF). The investigators not only found that greater weight loss was achieved with bariatric surgery over community weight management but patients who underwent surgery experienced greater and more rapid reduction in ICP. Furthermore, only patients in the surgical arm achieved a fall in ICP to ≤25 cm, which was associated with a mean weight loss of approximately 24% from their baseline weight. Dr. Ramsamy and colleagues highlight that surgery was not associated with statistically significant improvement in visual outcomes or headache, which are the most disabling symptoms of IIH. In response, Dr. Mollan and their coinvestigators note the study was powered to demonstrate a treatment effect for the primary outcome of ICP reduction (as a biomarker of disease remission), rather than for secondary outcomes regarding visual or other symptoms of IIH. That said, the investigators admit there remains no consensus definition for clinical remission in IIH. Dr. Brenner also comments on the potential adjuvant use of caffeine in weight loss for patients with IIH and the benefits of optic nerve sheath fenestration when vision loss occurs. The investigators cite their original manuscript (published in *JAMA Neurology*), which reported a rapid and significant fall in ICP within 2 weeks of bariatric surgery. It is possible that acute hormonal changes after surgery such as a rapid rise in gut neuropeptide glucagon-like peptide-1 may have played a larger role in ICP reduction than weight loss alone.

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Reader Response: Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension

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Mollan et al. report that bariatric surgery was superior to community weight management (CWM) regarding weight lost, intracranial pressure (ICP) reduction, disease remission, and quality of life in women with idiopathic intracranial hypertension (IIH).[1,2] They recommend for clinicians to have low thresholds of referral for bariatric surgery.[1]

However, surgery did not have a greater effect on papilledema grade, visual function, or headache disability than CWM.[3] More specifically, there was no difference in visual acuity, contrast sensitivity, perimetric mean deviation, or optic nerve and the retinal nerve fiber layer. Given that loss of vision is the most severe complication in IIH, and headache is the principal symptom, not

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highlighting these supplementary data in either the initial or follow-up paper seems to be a crucial omission. In particular, defining disease remission only in opening pressure or ICP reduction could be misleading.

In addition, although physical functioning and general health seemed to improve more in the surgery arm of the study (though we note no correction for multiple comparisons), this was not the case in emotional wellbeing, anxiety and depression, social functioning, or pain. Bariatric surgery, despite its potential risks, does have proven long-term health benefits.[4] However, its role in IIH treatment remains far from clear.

1. Mollan SP, Mitchell JL, Yiangou A, et al. Association of amount of weight lost after bariatric surgery with intracranial pressure in women with idiopathic intracranial hypertension. *Neurology*. 2022;99(11):e1090-e1099. doi:10.1212/WNL.0000000000200839.
2. Mollan SP, Mitchell JL, Ottridge RS, et al. Effectiveness of bariatric surgery vs community weight management intervention for the treatment of idiopathic intracranial hypertension: a randomized clinical trial [published correction appears in JAMA Neurol. 2021;78(7):882]. *JAMA Neurol*. 2021;78(6):678-686. doi:10.1001/jamaneurol.2021.0659.
3. Friedman DI. Bariatric surgery in patients with idiopathic intracranial hypertension: the silver bullet? *JAMA Neurol*. 2021;78(6):652-654. doi:10.1001/jamaneurol.2021.0364.
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Author Response: Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension

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We thank Ramsamy et al. for their comments. Idiopathic intracranial hypertension (IIH) is a systemic metabolic disease and has an established association with obesity. IIH has a detrimental effect on quality of life because most recipients experience headache.[1]

There are few IIH randomized clinical trials (RCTs), and the choice of a primary endpoint to determine a successful outcome varies between intracranial pressure (ICP) and visual function.[1] The IIH Weight Trial hypothesis was based on which method of weight loss would be superior for sustained ICP reduction and weight loss and was powered accordingly.[2] Ramsamy et al.'s critique may be based on their assumption that the trial was powered for secondary outcomes, which it was not, or their preference for visual function as the only outcome measure.[3] We chose the diagnostic criteria threshold for ICP to determine remission. There is no consensus definition for clinical remission in IIH. The results were reported according to the prespecified statistical analysis plan, and hence, this represents a low risk for reporting bias.[4]

When designing RCTs, choosing the most relevant primary and secondary trial outcomes is key and involves many stakeholders. Weight loss methods in IIH were determined by patient partners and experts and form part of the top 10 research priorities for IIH,[5] which this trial addresses.

1. Mollan SP, Sinclair AJ. Outcomes measures in idiopathic intracranial hypertension. *Expert Rev Neurother*. 2021;21(6):687-700. doi:10.1080/14737175.2021.1931127.
2. Mollan SP, Mitchell JL, Ottridge RS, et al. Effectiveness of bariatric surgery vs community weight management intervention for the treatment of idiopathic intracranial hypertension: a randomized clinical trial. *JAMA Neurol*. 2021;78(6):678-686. doi:10.1001/jamaneurol.2021.0659.
3. Ottridge R, Mollan SP, Botfield H, et al. Randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of idiopathic intracranial hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol. *BMJ Open*. 2017;7(9):e017426. doi:10.1136/bmjopen-2017-017426.
4. Ramsamy S, Singhal S, Patel R, Gruener A. Reader response: Association of amount of weight lost after bariatric surgery with intracranial pressure in women with idiopathic intracranial hypertension. *Neurology*. 2023;100(11):542-543.
5. Mollan S, Hemmings K, Herd CP, et al. What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals. *BMJ Open* 2019;9:e026573. doi:10.1136/bmjopen-2018-026573.

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Reader Response: Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension

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I read the article by Mollan et al.[1] regarding weight loss and intracranial hypertension (IH) with interest. Gastric bypass results in decreased dicarbonyl stress (DS).[2] DS-related compounds, such as methylgloxal, are associated with the breakdown of the blood-brain barrier,[3] as seen in IH through the glycation of biomolecules and the production of advanced glycation end products (AGEs).[3,4] Inhibiting semicarbazide-sensitive amine oxidase, which causes DS, with caffeine may lead to decreased weight gain and AGEs.[5]

Rapid weight loss through gastric surgery may alleviate the complications of IH; however, fenestration of the optic nerve sheath to avoid visual loss should be considered when there is progressive visual loss. Medical management of obesity may have more application in the future with continued progress in this field.

1. Mollan SP, Mitchell JL, Yiangou A, et al. Association of amount of weight lost after bariatric surgery with intracranial pressure in women with idiopathic intracranial hypertension. *Neurology*. 2022;99(11):e1090-e1099. doi:10.1212/WNL.0000000000200839.
2. Maessen DE, Hanssen NM, Lips MA, et al. Energy restriction and Roux-en-Y gastric bypass reduce postprandial α-dicarbonyl stress in obese women with type 2 diabetes. *Diabetologia*. 2016;59(9):2013-2017. doi:10.1007/s00125-016-4009-1.
3. Lissner LJ, Wartchow KM, Rodrigues L, et al. Acute methylglyoxal-induced damage in blood-brain barrier and hippocampal tissue. *Neurotox Res*. 2022;40(5):1337-1347. doi:10.1007/s12640-022-00571-x.
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We welcome Dr. Brenner's hypothesis regarding the mechanisms of how weight loss reduces intracranial pressure (ICP). Bariatric surgery has been shown to significantly reduce ICP in association with the amount of weight loss, in IIH,[1] which is most notable after Roux-En-Y Gastric Bypass (RYGB).[2]

Another potential mechanism is regarding the gut neuropeptide glucagon-like peptide-1 (GLP-1), which promotes satiety and weight loss. After RYBG, the bypassed food in the mid/distal jejunum exposes L-cells to nutrients and results in a sharp rise in GLP-1, oxyntomodulin, and peptide YY. Early improvements in glycemic control at 2 weeks post-RYGB in type 2 diabetes mellitus were linked to increased postprandial GLP-1, oxyntomodulin, and peptide YY secretion.[3]

We observed that ICP was rapidly reduced after bariatric surgery, which seemed to be independent of weight loss, because only relatively small changes in body weight occurred within 2 weeks.[1,2] Exenatide, a GLP-1 receptor agonist, directly reduces the CSF secretion and ICP in vivo. A randomized controlled trial demonstrated that exenatide significantly reduced ICP in active IIH at 2.5 hours, 24 hours, and 12 weeks.[4] Therefore, we believe the reduction in ICP observed at 2 weeks could be driven by GLP-1 and has the potential—after further investigation—to rival the current surgical practices to save vision in fulminant IIH.

Author disclosures are available upon request (journal@neurology.org).

1. Mollan SP, Mitchell JL, Ottridge RS, et al. Effectiveness of bariatric surgery vs community weight management intervention for the treatment of idiopathic intracranial hypertension: a randomized clinical trial. *JAMA Neurol*. 2021;78(6):678-686. doi:10.1001/jamaneurol.2021.0659.
2. Mollan SP, Mitchell JL, Yiangou A, et al. Association of amount of weight lost after bariatric surgery with intracranial pressure in women with idiopathic intracranial hypertension. *Neurology*. 2022;99(11):e1090-e1099. doi:10.1212/wnl.0000000000200839.
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CORRECTIONS

Clinically Relevant Changes for Cognitive Outcomes in Preclinical and Prodromal Cognitive Stages

Implications for Clinical Alzheimer Trials

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In the Research Article entitled "Clinically Relevant Changes for Cognitive Outcomes in Preclinical and Prodromal Cognitive Stages: Implications for Clinical Alzheimer Trials" by Borland et al.,[1] under the Cognitive Tests section, the sentence "Further explanation of tests, what they assess, and how points are counted are described in eMethods." should include the following link to the eMethods: links.lww.com/WNL/C167. The publisher regrets the omission.

Reference

1. Borland E, Edgar C, Stomrud E, Cullen N, Hansson O, Palmqvist S. Clinically relevant changes for cognitive outcomes in preclinical and prodromal cognitive stages: implications for clinical Alzheimer trials. *Neurology*. 2022;99(11):e1142-e1153. doi:10.1212/wnl.0000000000200817.

Juvenile Myoclonic Epilepsy 25 Years After Seizure Onset

A Population-Based Study

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In the Research Article entitled "Juvenile Myoclonic Epilepsy 25 Years After Seizure Onset: A Population-Based Study" by Camfield et al.,[1] the second sentence of the Discussion section of the Abstract should read, "All seizure types in juvenile myoclonic epilepsy (JME) resolved in 26%, and for 13%, only myoclonus persisted." In addition, the third sentence of the Discussion section should read, "All seizure types remit in approximately 26%, and in 13%, only myoclonic seizures persist for up to 22 years after stopping AEDs." The authors regret the errors.

Reference

1. Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. *Neurology*. 2009;73(13):1041-1045. doi:10.1212/wnl.0b013e3181b9c86f.

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